Objectives

- To diagnose common and uncommon soft tissue tumors in children and adolescents
- To formulate a differential diagnosis using a morphologic pattern-oriented approach
- To understand the use of ancillary molecular, cytogenetic, and immunohistochemical techniques in diagnosis and prognosis
- To review pertinent clinical, prognostic, genetic, and syndromic associations for specific neoplasms

Childhood and Adolescent Soft Tissue Tumors

- Relatively frequent compared with adults
- Many different diagnostic entities
- Majority benign or intermediate
- Soft tissue sarcomas comprise 7% of childhood cancers (5th in frequency)

World Health Organization, 2002

- Revised classification of soft tissue and bone tumors
- Histological categorization based on resemblance to defined tissue types
- Biologic potential categories: benign, intermediate (locally aggressive), intermediate (rarely metastasizing), malignant
- Emphasis on pathology and genetics

Kiel Pediatric Tumor Registry
Soft Tissue Sarcomas, 1687 Cases, 1977-1991

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyosarcoma</td>
<td>45%</td>
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<tr>
<td>Ewing sarcoma/PNET</td>
<td>23%</td>
</tr>
<tr>
<td>MPNST</td>
<td>7%</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>6%</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>4%</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>2%</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>2%</td>
</tr>
<tr>
<td>Malignant rhabdoid tumor (extrarenal)</td>
<td>1%</td>
</tr>
<tr>
<td>Other sarcomas</td>
<td>8%</td>
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</tbody>
</table>
SEER Registry, Soft Tissue Sarcomas
2182 neoplasms, 0-20 y.o., 1975-1995

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Rhabdomyosarcoma</td>
<td>39%</td>
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<tr>
<td>Dermatofibrosarcoma</td>
<td>9%</td>
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<tr>
<td>Malignant fibrous histiocytoma</td>
<td>7%</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>6%</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor</td>
<td>6%</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>5%</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>4%</td>
</tr>
<tr>
<td>Other or unspecified</td>
<td>21%</td>
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Grading of NRSTS

- Prognostic indicator for the degree of malignancy and possibility of metastases
- Based on mitotic rate, necrosis, histologic type, and extent of differentiation
- Grading systems:
  - POG (Parham), based on NCI system
  - FNCLCC (Coindre), based on adult data

Pathologic Evaluation of Soft Tissue Tumors

- Approach to fresh specimen
- Gross examination
- Histologic examination
- Differential diagnosis and selection of ancillary tests
- Pathology report and communication

Tumor Triage

1. Histology
2. Immunohistochemistry
3. Cytogenetics
4. Molecular tests
5. Flow cytometry
6. Other ancillary tests (i.e., EM)
7. Research

Ancillary Tests

- Immunohistochemistry
- Genetic tests
- Flow cytometry
- Electron microscopy
- DNA microarrays
- Proteomics
**Immunohistochemical Tests**
- Vimentin, SMA, MSA, desmin
- h-caldesmon, myogenin, MyoD1
- S100, Leu7, NF, GFAP, HMB-45, melan A
- CD34, CD31, HHV-8
- Cytokeratins, EMA, bcl-2
- CD99, Fli-1
- TdT, CD43, CD79a, others
- ALK-1, INI-1, WT1

**Genetic Tests for NRSTS**
- Conventional cytogenetics: global information
- FISH: localizes breakpoints
- RT-PCR: detects fusions
- Fusion or oncogene protein detection by immunohistochemistry

**The Pathology Report**
- Diagnosis (histologic type)
- Key information
  - Site
  - Type of resection or biopsy
  - Histologic grade (FNCLCC, POG, NCI)
  - Necrosis
  - Margins
  - Results of ancillary studies
- Familial, syndromic, or genetic implications
- Prognostic and therapeutic considerations

**Case 1. Alveolar rhabdomyosarcoma**
**Clinical History**
- 15 year old male with growing tumor of thenar eminence
- Fixed, firm, and limited to soft tissues
- MRI revealed an infiltrative, intramuscular lesion that did not invade bone

**Clinical History, cont.**
- Therapy was started with vincristine, actinomycin D, and cyclophosphamide.
- An experimental agent was added as window therapy.
- The lesion shrank and was excised.
- Consolidation therapy was given.
Case 1. Alveolar rhabdomyosarcoma

Clinical History, cont.

- Two years later, the patient presented with bone marrow and pulmonary metastases and expired shortly thereafter.
**Alveolar rhabdomyosarcoma**

A primitive malignant soft tissue neoplasm with round cell features that shows varying degrees of myogenesis and typically has fusions between PAX and FKHR genes.

WHO, 2002

**Rhabdomyosarcoma Diagnosis**
- Clinical characteristics
- Immunohistochemistry stains
- Molecular testing
- Differential diagnosis

**RMS Classification**
- Embryonal RMS (favorable risk)
  - Botryoid subtype
  - Spindle cell subtype
- Alveolar RMS (unfavorable risk)
  - Solid subtype
  - Mixed subtype

**Classification of RMS – Distinctions**
- Clinical
- Histological
- Immunohistochemical
- Molecular

**Clinical Features of RMS**

**ERMS**
- Young age (<5)
- Genitourinary tract
- Head and neck
- Odd sites (abdomen, bile duct)

**ARMS**
- Older age (adolescents)
- Extremities and axial muscles
- Parameningeal (particularly sinuses)
- Odd sites (breast, perianal)
**Histology of Typical RMS**

**ERMS**
- Loose and dense architecture
- Resemblance to fetal muscle
- Myxoid stroma
- Elongate cells

**ARMS**
- Septa
- Picket row arrangement
- “Floating” central clusters

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**Histology of Solid ARMS**

- Solid sheets of cells
- Round nuclei
- Lymphoma-like
- Don’t confuse with “dense” foci in ERMS – cytology is key

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**Rhabdomyosarcoma Immunohistochemical Features**

- Desmin
- MyoD
- Myogenin

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**Rhabdomyosarcoma Histology**

*From: WHO Classification of Tumours: Tumors of Soft Tissue and Bone, IARC Press, Lyon, 2002*
Rhabdomyosarcoma Differential Diagnosis

- Small round blue cell tumors
  - To be discussed with Case 2
- Myogenic tumors

Malignant Pediatric Myogenic Tumors

- Leiomyosarcoma (rare in pediatrics)
- Wilms’ tumor and other primitive organoid lesions
- Malignant peripheral nerve sheath tumor with rhabdomyomatous elements (Triton tumor)

Myogenic organoid tumors

- Wilms tumor
- Pleuropulmonary blastoma
- Hepatoblastoma
- Immature teratoma
- Ectomesenchymoma
Myomatous Wilms tumor

Myomatous Wilms’ tumor – botryoid features

Ectomesenchymoma

Pleuropulmonary blastoma with botryoid features

NSE, rosettes

myoblasts

Malignant Triton tumor

Benign Myogenic Tumors

- Juvenile rhabdomyoma
- Adult rhabdomyoma
- Genital rhabdomyoma
- Neuromuscular choristoma (benign Triton tumor)
- Accessory muscle
**Rhabdomyosarcoma Molecular Testing**

- **PAX3/FKHR [t(2;13)]**
  - ARMS exclusively
  - May be negative
- **PAX7/FKHR [t(1;13)]**
  - Younger age?
  - Mixed histology?
  - Better prognosis?
- **PAX-negative ARMS?**

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**Fusion-Negative Alveolar Rhabdos**
(black dots on right graph)
Gene expression analysis

*Davicioni et al., Cancer Res 66:6936-69, 2006*
Case 2. Extraosseous Ewing sarcoma
Clinical Summary

- A 16-year old male presented with a large chest wall lesion, not arising from a rib.
- It involved the soft tissue of the chest and axilla.
- Work-up revealed no metastatic disease or bony involvement.

Case 2. Clinical photo
(From Parham: Pediatric Neoplasia, Lippincott-Raven, 1996)

Case 2. MRI
(From Parham: Pediatric Neoplasia, Lippincott-Raven, 1996)

Case 2. Clinical Follow-up

- Therapy was started with doxorubicin, vincristine, cyclophosphamide, and dactinomycin, alternating with ifosfamide and etoposide.
- The lesion dramatically decreased in size, with alleviation of symptoms.
- After 12 weeks of therapy, an excision of the mass was performed.
- The patient is currently free of disease 98 months after diagnosis.
Ewing sarcoma/PNET
A round cell sarcoma that shows varying degrees of neuroectodermal differentiation (none in Ewing sarcoma), affects bone and soft tissue, and possesses a fusion between EWS and the ETS family of genes
WHO, 2002

Ewing Sarcoma Diagnosis
- Clinical characteristics
- Immunohistochemistry stains
- Molecular testing
- Differential diagnosis
Ewing Sarcoma (EFT) Histology

- Typical
- Atypical
- PNET
- Not prognostic with current therapy

Typical Histology
- Sheets of primitive, evenly round cells with abundant glycogen (bubbly on H and E)
- Inconspicuous nucleoli
- Few mitoses
- Light and dark cells

Atypical Histology
- Larger, irregular cells
- More prominent nucleoli
- More mitotic activity
- More likely to stain with neural markers

PNET
- Homer Wright rosettes
- Flexner rosettes
- Ganglionic differentiation
- Neuropil is very rare (cf. NBL)

Ewing’s Sarcoma – Clinical Features

- Adolescents and young adults
- Second most common malignant bone tumor
- Second most common malignant soft tissue tumor
- Prominent soft tissue mass, even with bone primary

Ewing Sarcoma – Locations

- All bones, particularly femur and pelvis
- Paravertebral
- Chest wall (Askin tumor)
- Peripheral nerve
- Unusual locations (meningeal, head and neck)
Ewing Sarcoma – Immunostains

- “Ewing’s markers”
  - CD99
  - Fli-1
- Neural markers
  - NSE
  - Synaptophysin
- Epithelial markers
  - Cytokeratin (10% of cases)
- Glial markers (rare)
  - GFAP
  - S100
- Desmin - rare

EFT Immunostains (From Parham: Pediatric Neoplasia, Lippincott-Raven, 1996)

Cytokeratin
Synaptophysin

Ewing Sarcoma Diagnosis

- Molecular markers
  - EWS/FLI1 [t(11;22)] 90%
  - EWS/ERG [t(21;22)] 10%
  - Other EWS/ETS Rare

EWS/FLI1 fusion

- Produces differently-sized fusion proteins, depending on site of fusion
  - Type 1, type 2, etc.
- Capable of causing downstream cascade of neuroectodermal differentiation
  - Cell of origin?
- Supports tumorigenic effects

Ewing sarcoma prognosis

- Bad genetic features
  - Non-type 1 fusion
  - p53 mutation
  - p16/p14ARF deletion

Differential diagnosis – the small round blue cell tumor

Neural crest
Differential diagnosis
Small round blue cell tumors, usual
- Rhabdomyosarcoma
- Neuroblastoma
- Non-Hodgkin lymphoma
- High grade synovial sarcoma
- Blastemal embryonal tumors, eg. Wilms, hepatoblastoma

Alveolar rhabdomyosarcoma

Neuroblastoma (CD99 negative)

Primitive Synovial Sarcoma

Cytokeratin

Lymphoblastic lymphoma

CD3

CD45

Blastemal Wilms tumor – serpentine pattern
Small Round Cell Tumors, Unusual

- Desmoplastic small round cell tumor
- Extramedullary leukemia
- Malignant peripheral nerve sheath tumor
- Small cell osteosarcoma
- Mesenchymal chondrosarcoma

Desmoplastic small round cell tumor

Extramedullary leukemia (AML M5)

MPNST – small cell

Small cell osteosarcoma

Mesenchymal chondrosarcoma
**Ewing Sarcoma Diagnosis**

- EM may be helpful in selected cases, particularly with confusing immunostains.
- Never rely on a single immunostain; always use a panel.
  - Both CD99 and Fli-1 are positive in NHL and other tumors.
  - CD45 may be negative in lymphoblastic lymphoma of bone and soft tissue!

**Case 3: Kaposiform Hemangioendothelioma**

- 7 month old female
- Vascular mass on jaw
- Multiple capillary hemangiomas, abdomen and thigh
- Anemia, thrombocytopenia
- History of tracheal obstruction, tracheostomy

**Clinical Course**

- No response to interferon, systemic steroids, embolization
- Intralesional steroids, vincristine, and interferon started
- Biopsy performed
- Amicar administered
Immunohistochemical Findings

- Positive for CD31, CD34, VEGF-R, SMA
- Mib-1 reactivity in 20% of nuclei
- Negative for Glut-1, VEGF-C, D2-40, Lewis Y, HHV-8
Kaposiform Hemangioendothelioma

Kaposiform hemangioendothelioma is a locally aggressive, immature vascular neoplasm, characterized by a predominant Kaposi sarcoma-like fascicular spindle cell growth pattern.

-WHO, 2002

Points for Discussion

- Differential diagnosis
- Comparative features of KHE and TA
- Kasabach-Merritt phenomenon
- Therapy-related changes

Kaposiform Hemangioendothelioma (KHE)

- Locally aggressive, non-metastasizing, immature vascular neoplasm
- Infancy and childhood (first decade)
- Males and females equally affected
- Retroperitoneum, skin, head/neck
- Ill-defined plaque-like mass
- Gradual, but incomplete regression

Differential Diagnosis

- Infantile hemangioma
- Tufted angioma
- Kaposi sarcoma
- Lymphangioma
KHE and TA

- Similarities: multinodular architecture, dilated lymphatic spaces, hemosiderin, microthrombi
- Differences: size, site, spindle cell fascicles, consumption coagulopathy

KS, CD34

KS, HHV-8
Kasabach-Merritt Syndrome

- Consumption coagulopathy
- Thrombocytopenia, anemia, hypofibrinogenemia
- Also associated with large vascular malformations, hemangiomas, chorangiomas
- Activated clotting within tumor vessels

Residual Vascular Lesions in Treated Kasabach-Merritt Syndrome

- KHE more frequent during active phase of consumption coagulopathy
- TA more common in residual lesions
- Therapy-related changes include fibrosis and lymphatic spaces

*Enjolras et al, 2000

Summary

- Kaposiform hemangioendothelioma
- Morphologic overlap with tufted angioma
- Association with Kasabach-Merritt syndrome
- Therapy-related morphologic changes
- Differential diagnosis

Case 4: Synovial Sarcoma

- 16-year old female
- Right anterior tibial soft tissue mass
- Biopsy
Synovial sarcoma

Synovial sarcoma is a mesenchymal spindle cell tumor which displays variable epithelial differentiation, including glandular formation and has a specific chromosomal translocation t(x;18)(p11;q11).

-WHO, 2002

- 5-10% of soft tissue sarcomas
- 42% of non-RMS in children
- >95% juxta-articular (knee, ankle)
- Unusual sites: head/neck, chest, abdomen, retroperitoneum
- Peak incidence in second decade
Points for Discussion

- Histologic variants
- Immunohistochemistry
- Genetic aberrations
- Pathologic-prognostic factors
- Differential diagnosis

Histologic Variants

- Biphasic
- Monophasic
- Small cell
- Rhabdoid
- Myxoid
- Calcifying
- Poorly differentiated

Immunohistochemistry

- Epithelial markers: cytokeratins (AE1/AE3, CAM 5.2, CK7, CK19), epithelial membrane antigen, tight junction-related proteins
- Mesenchymal markers: CD56, CD57, CD99, S100 protein, neurofilament, type IV collagen, actins, vimentin
- Epidermal growth factor receptor
- bcl-2 overexpression
- Oncogene overexpression: p53, Her2/neu

SS Genetic Abnormalities

- t(x;18)(p11.2;q11.2)
- SYT-SSX fusion
- SSX has closely related genes on Xp11: SSX1, SSX2, SSX4
- Prognostic significance questioned

Pathologic – Prognostic Factors

- Size
- Grade (mitotic rate, % necrosis)
- Histologic subtype
- Stage (metastases, resectability, margins)
- Ploidy
- p53 overexpression
- Mast cells

Differential Diagnosis

- Malignant peripheral nerve sheath tumor
- Ewing sarcoma/PNET
- Fibrosarcoma
- Leiomyosarcoma
- Dermatofibrosarcoma protruberans
- Rhabdomyosarcoma
- Malignant rhabdoid tumor
- Carcinoma
Infantile Fibrosarcoma, TEL rearrangement

Leiomyosarcoma
Summary

- Synovial sarcoma
- Immunohistochemical profile
- Genetic abnormalities
- Prognostic factors
- Nosology uncertain
Case 5: Gardner Fibroma and Desmoid Fibromatosis

- 12-year old boy
- Superficial soft tissue masses since 2 years of age: paraspinal, thoracic, posterior thigh, head
- Painful, enlarging paravertebral mass

Family History

- Paternal uncle: rhabdomyosarcoma
- Paternal grandfather and others: colonic adenocarcinoma
- Father: adenomatous polyposis coli, mesenteric desmoid fibromatosis
Gardner Fibroma

A benign soft tissue lesion consisting of thick, haphazardly arranged collagen bundles with interspersed bland fibroblasts, a plaque-like growth pattern with infiltration and entrapment of surrounding structures, and an association with desmoid-type fibromatosis and Gardner syndrome or adenomatous polyposis coli.

-WHO, 2002
Desmoid fibromatosis

Desmoid-type fibromatosis

A fibroblastic neoplasm that arises in deep soft tissues and is characterized by infiltrative growth and a tendency toward local recurrence, but an inability to metastasize.

-WHO, 2002

Desmoid fibromatosis

Desmoid-Fibromatosis

- Peak incidence in 2nd – 3rd decades
- Abdomen, head/neck region, extremities, shoulder girdle, trunk
- Local recurrence in 33-68%
- Clonal lesion
- Trisomies 8, 20, deletion of 5q

Familial Adenomatous Polyposis

- Caused by germline APC mutation:
  1/3 sporadic
  2/3 familial
- Average age of onset for intestinal adenomas is 25 years
- 100% lifetime risk of intestinal adenocarcinoma
Gardner Syndrome

A variant of familial adenomatous polyposis that includes epidermoid cysts, osteomas, dental anomalies, and desmoid tumors, in addition to colorectal adenomas.

- WHO, 2000

APC in Children

- Congenital hypertrophy of retinal pigment epithelium
- Epidermoid cysts
- Osteomas
- Dental abnormalities
- GAF and desmoid fibromatosis
- Hepatoblastoma
- Brain tumors
- Rhabdomyosarcoma
- Nasopharyngeal angiofibroma

Clinical Course

- APC mutation, exon 15
- Desmoids originating in sites of GAFs, thorax and back
- Intestinal surveillance: lymphoid hyperplasia followed by focal adenomatous change and tubular adenomas
- Colectomy

Lymphoid hyperplasia, colon

Tubular adenoma

Multiple polyps, colon
Differential Diagnosis: GAF and DES

- Scar, keloid
- Nuchal fibroma
- Fibrolipoma
- Fibromatoses
- Myofibrosarcoma
- Other sarcomas

Summary

- Diagnosis
- Risk for fibromatosis
- Association with APC
- Possible sentinel event

Case 6: Inflammatory Myofibroblastic Tumor

- 7-year old girl
- Anemia (Hgb 7.4 g/dl), thrombocytosis (1,070 x 10^3/uL) elevated ESR (142 mm/hr), elevated C-reactive protein (44.8 mg/dl)
- 11 cm abdominopelvic mass
- Resection

Inflammatory myofibroblastic tumor

Inflammatory myofibroblastic tumor

Inflammatory myofibroblastic tumor
Inflammatory myofibroblastic tumor

Inflammatory myofibroblastic tumor, ALK-1

**Inflammatory Myofibroblastic Tumor**

IMT is a distinctive lesion composed of myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils. It occurs primarily in soft tissue and viscera of children and young adults.

- WHO, 2002

**Infancy to adulthood, most frequent in first 3 decades**

- Mesentery, omentum, retroperitoneum, lung, mediastinum, head/neck, liver
- Clinical syndrome: fever, weight loss, growth failure, anemia, thrombocytosis, polyclonal hyperglobulinemia, elevated ESR
- Local recurrence in 25%
- Rare cases with malignant transformation and metastasis

**Points for Discussion**

- Terminology and diagnostic criteria
- Molecular and cytogenetic abnormalities
- Treatment and prognosis
- Differential diagnosis

**Inflammatory Myofibroblastic Tumor**

- Infancy to adulthood, most frequent in first 3 decades
- Mesentery, omentum, retroperitoneum, lung, mediastinum, head/neck, liver
- Clinical syndrome: fever, weight loss, growth failure, anemia, thrombocytosis, polyclonal hyperglobulinemia, elevated ESR
- Local recurrence in 25%
- Rare cases with malignant transformation and metastasis
Immunohistochemistry of IMT: Summary of Six Series

Genetic Abnormalities

- Chromosome 2p23 abnormalities with \textit{ALK} gene rearrangements
- Fusion oncogenes: tropomyosin (\textit{TPM3, TPM4}), clathrin (\textit{CLTC}), Ran-binding protein 2 (\textit{RANBP2}), \textit{CARS}, \textit{ATIC}, others
- Detection: immunohistochemistry, FISH, RT-PCR
- \textit{HMGIC} rearrangement
- Role of viruses

Significance of \textit{ALK} Rearrangements

- Further evidence of neoplastic nature
- Useful for differential diagnosis, in the appropriate clinicopathologic context
- Potential future therapeutic target
- But what about ALK-negative IMT?
How Specific Are ALK Rearrangements?*

- Rhabdomyosarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, and MFH have ALK abnormalities
- Not found in nodular fasciitis, desmoid, infantile myofibromatosis, GIST, splenic and lymph node inflammatory pseudotumors, or other spindle cell neoplasms
- ALK fusion partners include TPM, RanBP2, CLTC, and unidentified genes
- Staining pattern varies with fusion partners, may be antibody-dependent

*Cessna et al, 2002; Cook et al, 2001; Pulford, 2001; Lawrence, 2000

Treatment, Outcome, and Prognosis

- Treatment
  Surgery
  Pharmacotherapy (+)
- 25% recurrence rate for extrapulmonary IMT
- Rare metastases (<5%)
- “Malignant transformation”
- Potential prognostic factors: atypia, ganglion-like cells, p53 expression, aneuploidy?

Differential Diagnosis

- Inflammatory processes
- Calcifying fibrous tumor
- Desmoid fibromatosis
- Solitary fibrous tumor
- GIST
- Dendritic cell neoplasms
- Spindle cell sarcomas
- Sarcomatoid carcinoma and melanoma

Retroperitoneal fibrosis
Calcifying fibrous pseudotumor
Solitary fibrous tumor
Summary

- Inflammatory myofibroblastic tumor
- Intermediate biologic potential
- ALK abnormalities
- Persistent questions

Case 7. Lipoblastomatosis
Clinical History

- A 2 year-old boy presented with a tumor in the right buttock.
- The lesion had been present since birth and had been slowly growing.
- Examination revealed non-tender mass that appeared to be adherent to the underlying muscle and did not interfere with mobility.
- MRI studies indicated that the mass was infiltrative and had the density of fat.
Case 7. Lipoblastomatosis

Case 7. Clinical Follow-up

- The lesion was excised with narrow margins.
- A recurrence was noted at seven months and was excised with no further problems.
Lipoblastoma/Lipoblastomatosis

A lobulated, localized (lipoblastoma) or diffuse (lipoblastomatosis) tumor, resembling fetal adipose tissue.

WHO, 2002

Lipoblastoma vs. Lipoblastomatosis

- Lipoblastoma – non-invasive
- Lipoblastomatosis – invasive of underlying tissues

Lipoblastoma Clinical Features

- Bulky mass in young infant
- Mobile
- Radiographic features of fat
- Requires more aggressive surgery than lipoma to prevent recurrence

Lipoblastoma Routine Histology

- Lobulated mass with fibrous trabeculae
- Myxoid stroma
- Lipoblasts (eccentric nucleus, vacuolated cytoplasm) – defining cell type
- Typically mixed with mature fat
- Matures into lipoma with age

Lipoblastoma Immunostains

- S100 (stains all fatty tumors)
- Cytokeratin, mucin (rules out carcinoma/chordoma in questionable cases)
- Usually not needed

Benign Pediatric Lipomatous Tumors Differential Diagnosis

- Lipoma
- Lipoblastoma
- Lipofibromatosis
- Fibrous hamartoma of infancy
Lipoma

Lipofibromatosis

Fibrous hamartoma of infancy

Primitive mesenchyme

Malignant Pediatric Lipomatous Tumors and Mimics

- Liposarcoma (particularly myxoid variant)
- Mucinous carcinoma (particularly metastatic from colon)
- Myxofibrosarcoma
- Chordoma

Myxoid liposarcoma

Mucinous carcinoma
Molecular Tests

- CHOP/FUS \([t(12;16)]\) seen with myxoid and round cell liposarcoma, can be useful in questionable cases
- Chromosome 8q11-13 alterations common in lipoblastoma and affect \(PLAG1\) gene
  - May affect other lipomatous lesions?

Clinical management of lipoblastoma

- Requires more aggressive surgery than lipoma to prevent recurrence
- Prolonged follow-up (five years) may be necessary because of late recurrence.

Case 8. Clinical Summary

- A 6 month-old girl presented with intermittent seizures and multiple skin nodules located on her back, near the paraspinal region.
- The lesions were freely moveable and well-circumscribed, and they appeared to be primarily situated within the subcutaneous fat.
- An excisional biopsy was performed. and following the diagnosis, MRI
Case 8. Malignant rhabdoid tumor

Case 8. Clinical Summary, cont.

- CT scanning of the head revealed a paraventricular tumor located near the left parietal lobe.
- The lesion was isointense with grey matter had areas of apparent necrosis, cystic degeneration, and associated edema.
- Post-contrast images showed variable enhancement of the tumor.

Soft tissue rhabdoid tumor

A malignant tumor of infants and small children, characterized by neoplastic cells with large nucleoli, abundant, eccentric cytoplasm, and intracytoplasmic inclusions, the latter composed of intermediate filaments. An INI gene mutation is typically present.

WHO, 2002

Clinical Follow-up

- The lesion was excised but rapidly regrew with spinal cord metastases.
- The child expired four months after the initial diagnosis.
**Rhabdoid Tumor**

**Clinical Features**
- Infants in majority of cases
- Diverse locations
- Aggressive tumors with poor clinical outcome

**Rhabdoid Tumor Locations**
- Kidney
- CNS (primary, synchronous)
- Liver
- Axial soft tissues
- Skin (primary, metastatic)

**Rhabdoid Tumor**

**Immunohistochemical Features**
- Co-expression of vimentin and cytokeratin – confirmed by EM
- Lack of expression of HSNF5/INI1
- Other intermediate filaments and markers may be expressed (non-specificity?)

**Rhabdoid tumor**

**Molecular Features**
- Deletion of HSNF5/INI1
- Detected by FISH
- Immunostain detects absence of staining
- Important in chromatin remodeling
- Normally inhibits cyclin D1, leading to growth suppression

**INI1 caveats:**
- Different names used (hSNF5, SMARCB, BAF47)
- May be inactivated in choroid plexus tumors and epithelioid sarcoma
- Negative staining is diagnostic, not positive staining
Rhabdoid Tumor Diagnosis

- “True” rhabdoid tumor
- “Composite” rhabdoid tumor (CRT)

Rhabdoid Tumor Differential Dx Sarcoma

- Rhabdomyosarcoma
- Desmoplastic small round cell tumor
- Malignant peripheral nerve sheath tumor
- Epithelioid sarcoma
- Alveolar soft part sarcoma

DSRCT CRT

“Rhabdoid” rhabdomyosarcoma

MPNST CRT (epithelioid MPNST)

Epithelioid Sarcoma CRT
Alveolar soft part sarcoma

MRT Diagnosis - Non-sarcomas
- Carcinomas of various types
- Melanoma
- Neuroendocrine tumors
- Some benign tumors
  - Salivary gland
  - Meningioma

Carcinomatous CRT

MRT Diagnosis Requires:
- Proper clinical setting and
- Immunohistochemical confirmation or
- Genetic confirmation

Conclusions
- Morphologic basis for diagnosis
- Ancillary techniques useful when carefully chosen
- Pathologic-prognostic factors
- Syndromic associations
- Therapeutic implications
- Genetic studies

The Pathologist’s Role
- Diagnosis
- Ancillary tests
- Pathologic-prognostic features
- Differential diagnosis
- Multidisciplinary team member